Abstract

The cDNA sequence encoding porcine brain
natriuretic peptide and related genes encoding canine and
human peptides with natriuretic activity are disclosed.
The gene is shown to make accessible the DNAs encoding
analogous natriuretic peptides in other vertebrate species.
The genes encoding these NPs can be used to effect
modifications of the sequence to produce alternate forms of
the NPs and to provide practical amounts of these proteins.
The NPs of the invention can also be synthesized
chemically. The invention peptides have the formula:

R¹-Cys-Phe-Gly-Arg- Arg/ - Leu/ -Asp-Arg-Lys Met

Ile- Gly/ -Ser- Leu/ -Ser-Gly-Leu-Gly-Cys-R²
Ser Ser

wherein R¹ is selected from the group consisting of:

(H);

Gly-;

25 Ser-Gly-;

Asp/ Lys/ -Ser-Gly-; Gly

Arg/ Asp/ His/ - Lys/ -Ser-Gly-; Gln Gly

Arg/ Asp/
Met/ - His/ - Lys/ -Ser-Gly-;
Val Gln Gly

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Arg/
                                             Asp/
                       Thr/ - Met/ - His/ - Lys/ -Ser-Gly-;
                       Met
                              Val
                                      Gln
                                             Gly
5
                                      Arg/
                                             Asp/
                 Lys- Thr/ - Met/ - His/ - Lys/ -Ser-Gly-;
                       Met
                              Val
                                      Gln
                                             Gly
                                      Arg/
                                             Asp/
             Pro-Lys- Thr/ - Met/ - His/ - Lys/ -Ser-Gly-;
                       Met
                              Val
                                      Gln
                                             Gly .
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                                      Arg/
                                             Asp/
         Ser-Pro-Lys- Thr/ - Met/ - His/ - Lys/ -Ser-Gly-;
                       Met
                              Val
                                     Gln
                                             Gly
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or a 10- to 109-amino acid sequence shown as the native upstream sequence for porcine, canine or human BNP in Figure 8, or a composite thereof;

R² is (OH), NH₂, or NR'R" wherein R' and R" are independently lower alkyl (1-4C) or is

Asn/ Lys 20 Asn/ -Val Lys Asn/ -Val-Leu Lys 25 Asn/ -Val-Leu-Arg Lys Asn/ -Val-Leu-Arg- Arg/ Lys Lys Asn/ -Val-Leu-Arg- Arg/ - Tyr/ Lys Lys 30 or the amides (NH, or NR'R") thereof, with the proviso that if formula (1) is

R¹-Cys-Phe-Gly-Arg-Arg-Leu-Asp-Arg-Ile-Gly-Ser-Leu-Ser-Gly-Leu-Gly-Cys-R² and R^1 is Asp-Ser-Gly-, R^2 cannot be Asn-Val-Leu-Arg-Arg-Tyr.

The peptides of the invention can be formulated into pharmaceutical compositions and used to treat conditions associated with high extracellular fluid levels, especially congestive heart failure.

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